(51) International Patent Classification 5 : **A61B 5/00, 5/14, G01N 21/35**	**A1**	(11) International Publication Number: **WO 90/07905** (43) International Publication Date: 26 July 1990 (26.07.90)

(21) International Application Number: PCT/US90/00394

(22) International Filing Date: 17 January 1990 (17.01.90)

(30) Priority data:
298,904   19 January 1989 (19.01.89)   US

(71) Applicant: FUTREX, INC. [US/US]; P.O. Box 2398, 7845 Airpark Road, Gaithersburg, MD 20879 (US).

(72) Inventors: ROSENTHAL, Robert, D. ; 9805 Hallowell Place, Gaithersburg, MD 20879 (US). PAYNTER, Lynn, N. ; 7886 Marioak Drive, Elkridge, MD 21227 (US). MACKIE, Linda, H. ; 1607 Bradley Drive, Rockville, MD 20851 (US).

(74) Agents: ROTHWELL, G., Franklin et al.; Bernard, Rothwell & Brown, 1700 K Street, NW, Suite 800, Washington, DC 20006 (US).

(81) Designated States: AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH (European patent), CM (OAPI patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GA (OAPI patent), GB (European patent), HU, IT (European patent), JP, KP, KR, LK, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), MW, NL (European patent), NO, RO, SD, SE (European patent), SN (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent).

Published
With international search report.
With amended claims.

(54) Title: NON-INVASIVE MEASUREMENT OF BLOOD GLUCOSE
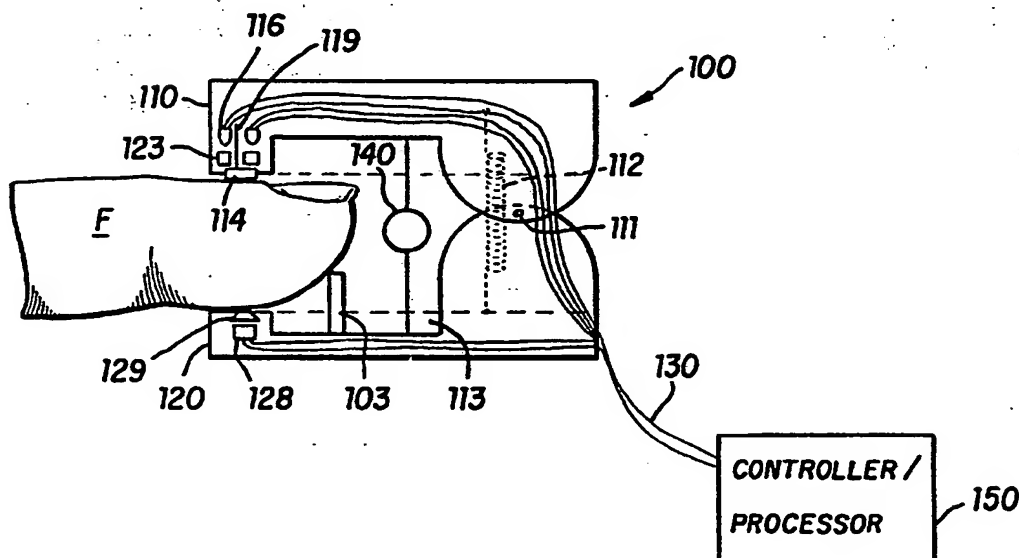
(57) Abstract

Near-infrared quantitative analysis instruments (100) and methods non-invasively measure blood glucose by analyzing near-infrared energy following interactance with venous or arterial blood, or transmission through a blood containing body part (F). The instruments and methods are accurate and readily lend themselves to at-home testing by diabetics.

1

NON-INVASIVE MEASUREMENT OF BLOOD GLUCOSE

Field of the Invention

This invention relates to instruments and methods
for the non-invasive quantitative measurement of blood
5   glucose. More particularly, the invention relates to
such quantitative measurement via near-infrared
interactance and transmittance.

Background of the Invention

Information concerning the chemical composition of
10   blood is widely used to assess the health
characteristics of both people and animals. Blood
analysis provides an indication of the current status
of metabolism (e.g. glucose content) as well as level
of risk associated with certain major illnesses (e.g.
15   risk of cardio-vascular disease as a function of
cholesterol level). Blood analysis, by the detection
of above or below normal levels of various substances
also provides direct indication of the presence of many
types of diseases and dysfunctions.
20   The normal method of determining blood chemistry
is by removing a sample of blood (e.g. 5-10 ml) and
performing one or more standard chemical tests. These
types of tests are moderately expensive, require one
class of trained technicians to remove the blood and
25   another class of trained technicians to perform the
chemical tests. Moreover, the results of the blood

tests often are not available for several hours, and
sometimes even several days.

Recently, an alternative type of technology (i.e.
self-contained instruments) has been introduced for
5   relatively rapid blood screening of a large number of
subjects. These instruments, in general, use a much
smaller blood sample (approximately .25 ml) from a
"finger poke." This small blood sample is placed on a
chemically-treated carrier and entered into the
10   instrument. These instruments normally provide either
an individual analyses (e.g. glucose level) or multiple
analysis in a few moments. These types of instruments
unfortunately are quite costly, e.g., in the range of
several thousand dollars.

15   A third class of blood instrumentation is
available for the specific purpose of determining
glucose level in people with diabetes. This technology
also uses a small sample from a finger poke and the
sample is placed on a chemically treated carrier which
20   is inserted into a portable battery operated
instrument. In general, these instruments provide a
single function; i.e. measurement of glucose. Although
these specialized instruments are relatively low cost
($300 or less is typical), the cost of the disposable
25   carrier "stick" must be considered. Since some
diabetic patients may require glucose analysis four or
more times a day, the cost over a period of a year can
become significant.

Current glucose analytical systems require blood
30   to be extracted from the body prior to performing the
analysis. This blood withdrawal requirement limits the
application of such testing; many people who may be
interested in knowing their glucose level are reluctant
to have either their finger poked or blood samples

removed by hypodermic needle. This reluctance or anxiety in allowing blood sample removal is due to concern over the possibility of infection, discomfort (pain) and generalized patient fear.

5   Thus, there is a great need for non-invasive analytical instruments and methods that would provide essentially the same accuracy as conventional blood glucose tests. Moreover, there is a need for a non-invasive low-cost method for measurement of glucose in

10   diabetic patients.

    Near-infrared (sometimes referred to herein as simply "near-IR") quantitative analysis is widely used in the field of agriculture for determining chemical compositions within grain, oilseeds, and other

15   agricultural products. As an example, near-IR energy reflected from the surface of finely ground seeds and grain provides information concerning protein and moisture content. For a general introduction to near infrared quantitative analysis, see "An Introduction to

20   Near-Infrared Quantitative Analysis" presented by Robert D. Rosenthal at the 1977 Annual Meeting of American Association of Cereal Chemists. Near-infrared technology has been extended to allow totally non-destructive measurements by using light transmission

25   through a sample as discussed in "Characteristics of Non-Destructive Near-Infrared Instruments for Grain and Food Products" by Robert D. Rosenthal, presented at the 1986 Meeting at the Japan Food Science Institute. Although this transmission approach avoids the need to

30   finely grind the sample, it is not suited for use where access to two opposite surfaces is not available.

    One example of this transmission approach is provided in U. S. Patent No. 4,621,643 (New, Jr. et al., 1986) relates to an optical oximeter apparatus for

determining pulse rate and degree of arterial oxygen
saturation. Light energy is passed through an
appendage of the body, e.g. a finger, and strikes a
detector positioned on a side of the appendage opposite

5   from the light source. Pulse rate and saturated oxygen
are calculated from coefficients of extinction of light
at the selected wavelengths.

        Another approach to near-infrared quantitative
analysis, using near-infrared interactance, was

10   developed for non-invasively measuring body fat
content. This approach is described in "A New Approach
for the Estimation of Body Composition: Infrared
Interactance", Joan M. Conway et al., The American
Journal of Clinical Nutrition, 40: Dec. 1984, pages

15   1123-1230. In this non-invasive technique, a small
optical probe that allows optical energy to enter the
arm is placed on the biceps. The percent body fat of
the entire body is determined by measuring the spectrum
change of the energy returned from an area adjacent the

20   light entry point.

Summary of the Invention

        In accordance with the present invention, a near-
infrared quantitative analysis instrument for measuring
blood glucose comprises means for introducing near-IR

25   energy into blood present in a body part of a subject,
means for detecting near-IR energy emerging from the
subject, means for converting an electrical signal
corresponding to the detected energy into a readout
indicative of the quantity of glucose present in the

30   blood of the subject, and means for positioning the
introducing means and detecting means adjacent to the
body part of the subject.

The present invention also provides methods for the near-infrared quantitative analysis of blood glucose, these methods including the steps of introducing near-IR energy into the blood within a body
5 part of a subject, detecting near-IR energy emerging from the subject, the detector providing an electrical signal upon detecting said emerged energy, and processing the electrical signal to provide a second signal indicative of the amount of glucose present in
10 the blood. Some of these inventive methods utilize the principal of near-IR transmission while others utilize the principal of near-IR interactance.

In accordance with one aspect of the present invention, a near-infrared quantitative analysis
15 instrument for measuring blood glucose comprises means for introducing near-IR energy into blood present in a blood vessel, means for detecting near-IR energy following interactance of the same with the blood, and means for positioning the introducing means and
20 detecting means over a blood vessel of the subject.

This aspect of the invention further relates to methods wherein near-IR energy is introduced into a vein or artery of a subject and interacts with blood glucose, the near-IR energy emerging from the subject
25 is detected by a detector which provides an electrical signal, and the signal is processed to provide a readout indicative of the amount of glucose in the blood.

This aspect of the invention also relates to means
30 and methods for marking a position over a vein or artery of a subject and then aligning a near-IR analysis instrument with the markings to accurately position the instrument.

Another aspect of the invention relates to an
apparatus for measuring blood glucose via near-IR
transmission through a blood-containing body part, the
apparatus including means for introducing near-IR
5   energy into one side of a body part, means for
detecting near-IR energy emerging from an opposite side
of the body part and means for positioning the near-IR
introducing and detecting means on opposite sides of
the body part.

10   This aspect of the invention also relates to
methods for measuring blood glucose via near-IR
transmission including the steps of introducing near-IR
energy into one side of a blood-containing body part,
detecting near-IR energy emerging from an opposite side

15   of the body part and calculating blood glucose content.

Brief Description of the Drawings

FIG. 1 is a partially schematic elevational view
of a near-infrared quantitative blood analysis
instrument to which the present invention pertains.

20   FIGS. 2A and 2B are partially schematic
elevational views of alternate embodiments of near-
infrared quantitative analysis instruments.

FIG. 3 is an elevational view of a location device
for use with the instrument shown in FIG. 1.

25   FIG. 4 illustrates one embodiment for practicing
the inventive method.

FIG. 5 illustrates two known configurations for
interposing filters in a light path.

FIG. 6 is a plot of log (1/I) versus wavelength.

30   FIG. 7 illustrates a wavelength search study via a
plot of correlation coefficient versus wavelength.

FIGS. 8A and 8B show plots of midpoint wavelength
versus correlation coefficient.

FIGS. 9 and 10 illustrate plots of correlation coefficient versus wavelength for first derivative equations.

5   FIGS. 11 and 12 illustrate plots of correlation coefficient versus wavelength for second derivative equations.

Detailed Description of the Preferred Embodiments

This invention uses the principle of light interactance to measure blood glucose level non-

10   invasively by locating an optical transmitter and a detector on the skin surface near either an artery or vein. Alternatively, the invention uses the principal of light transmission through a portion of the body that has relatively uniform profusion of blood in order

15   to measure non-invasively blood glucose.

In general, the arteries and veins of the human body are buried deep in the body to protect them from possible harm. However, in certain locations of the body, these blood carrying vessels are close to the

20   skin surface. This is particularly true for veins. Some examples of such locations are at the crease of the elbow, the wrist, the back of the hand, and the bridge of the nose. Since the concentration of glucose is relatively constant in both the veins and arteries,

25   valid measurements can be obtained in either. However, because veins are generally closer to the skin's surface, they usually are the better candidate for non-invasive measurements.

The finger tip is another site particularly well

30   suited for performing blood measurements with near-IR light. The blood supply is distributed within the finger tip and, thus, small variations in the placement

of a near-IR emitter or detector will not have a
profound effect on the measurement results.

According to one embodiment of the invention
utilizing near-IR interactance analysis techniques,
5   near-IR light energy at bandwidths centering on one or
more wavelengths of interest is passed through the skin
and connective tissues and into a blood vessel of a
subject. A portion of the energy re-emerges from the
blood vessel of the test subject and is detected by a
10   detector. Following amplification of the detector-
generated signal, the amplified output is processed
into an output signal indicating the amount of glucose
in the subject's blood. The output signal drives a
display device for providing a visual display of blood
15   glucose content.

According to another embodiment of the invention
utilizing near-IR transmission analysis techniques,
near-IR light energy at bandwidths centering on one or
more wavelengths of interest is transmitted through a
20   blood-containing portion of the body of a test subject.
The near-IR energy emerges from the test subject,
opposite from the near-IR source, and is detected by a
detector. Following amplification of the detector-
generated signal, the amplified output is processed
25   into an output signal indicating the amount of glucose
in the subject's blood.

In one embodiment utilizing near-IR interactance,
the entire analytical instrument, including near-
infrared source, transmitter, detector, amplifier, data
30   processing circuitry and readout is contained within a
lightweight hand-held unit. Infrared emitting diodes
(IREDs) disposed in one chamber of the unit are focused
to transmit near-IR energy of preselected wavelength(s)
to, e.g., a prominent vein of the wrist. The near-IR

energy interacts with the constituents of the venous
blood and is re-emitted from the vein. A detector
housed within a second chamber of the unit is disposed
along the vein a distance (1) from the emitter and
5   collects this energy. The detected signal is amplified
and data processed into a signal indicative of the
amount of glucose in the blood. This signal is then
fed to a readout device (preferably a digital readout)
for recordation by a technician or direct analysis by a
10   physician or the subject himself.

Other near-IR apparatus, such as the optical probe
and associated instrumentation described in U.S. Patent
No. 4,633,087 (Rosenthal), are useful in the practice
of the present methods in which near-IR interactance is
15   used to quantitatively measure blood glucose levels.

The present invention also includes a location
device specially adapted to permit the user to locate
the interactance instrument discussed above accurately
along a vein. The location device permits the skin to
20   be marked to ensure that repeated measurements are
taken from the same location, if desired.

A particularly preferred lightweight, hand-held
interactance analysis instrument in accordance with the
invention is illustrated in Fig. 1. The instrument 10
25   includes one or more means for providing at least one
point source of near-infrared energy of a predetermined
half-power bandwidth centered on a wavelength of
interest positioned within a first chamber 30 of the
instrument 10. The near-infrared point source means
30   are positioned so that near-infrared energy being
emitted from the point source means will be focussed by
lens 12 through window 14 and onto the skin of the test
subject. The near-infrared point source means may
comprise one or a plurality of infrared emitting diodes

(IREDs). Two such IREDs 16 are visible in the
embodiment illustrated in Fig. 1. In other embodiments
employing a plurality of IREDs, three, four or more
IREDs may be utilized as the point source means.

5   In lieu of laborious characterization and sorting of
each IRED, we prefer to provide narrow bandpass optical
filters (as shown schematically in Fig. 1) between the
infrared emitting diodes and the lens 12. A filter 23
is positioned between each IRED and lens 12 for

10   filtering near infrared radiation exiting each IRED and
thereby allowing a narrow band of near-infrared
radiation of predetermined wavelength to pass through
the filter and lens 12. Utilization of narrow bandpass
optical filters provides for specific wavelength

15   selection independent of the center wavelengths of the
particular infrared emitting diodes being used.
Measurements can be taken inside the half power
bandwidth of the IREDs, or alternatively, outside the
half power bandwidth of the IREDs as disclosed in

20   commonly owned U.S. Patent No. 4,286,327. Figure 5
illustrates two known configurations for interposing
filters in a light path.

        An optical detector, illustrated schematically and
designated by reference numeral 28, is disposed within

25   a lower end portion 42 of a second chamber 40 in case
20. Inner wall 22 is positioned between detector 28
and lens 12, thereby providing an optically-isolating
mask which prevents near infrared radiation from the
point source means and/or lens 12 from impinging

30   directly on detector 28. Optical detector 28 generates
an electrical signal when near-infrared radiation is
detected.

        The optical detector 28 is connected to the input
of an electrical signal amplifier 32 by suitable

electrical conducting means 33. Amplifier 32 may be an inexpensive integrated circuit (IC) signal amplifier, and amplifies the signals generated when near-IR energy strikes detector 28. The output of amplifier 32 is fed to a data processor and display driver 34 which provides a signal to readout device 36. The readout device 36 may have a digital display for directly displaying the amount of glucose present in the subject's blood.

The embodiment of Fig. 1 includes an optical filter 29 for shielding all but the desired near-IR energy from detector 28. Filter 29 and window 14 are positioned for direct contact with the skin of the test subject. An optically clear window can be employed in lieu of filter 29, if desired.

As noted earlier, this embodiment of the present invention utilizes the principal of near-IR interactance for quantitative analysis. In interactance, light from a source is shielded by an opaque member from a detector so that only light that has interacted with the subject is detected. Accurate measurements of the concentration of blood glucose can be made using many of the conventional algorithms used in near-IR quantitative analysis including those that have only a single variable term such as the following:

Approximated First Derivative Algorithm

$$C = K_o + K_1 [\log 1/I_G - \log 1/I_H]$$

Approximated Second Derivative Algorithm

$$C = K_o + K_1 [\log 1/I_A - 2*\log 1/I_B + \log 1/I_C]$$

Normalized First Derivative Algorithm

$$C = K_o + K_1 \frac{[\log 1/I_G - \log 1/I_H]}{[\log 1/I_I - \log 1/I_J]}$$

5

Normalized Second Derivative Algorithm

$$C = K_o + K_1 \frac{[\log 1/I_A - 2*\log 1/I_B + \log 1/I_C]}{[\log 1/I_D - 2*\log 1/I_E + \log 1/I_F]}$$

where C denotes concentration of glucose present in the

10   blood, K_0 is the intercept constant, K_1 is the line
slope of the variable term, and log 1/I terms are as
defined in Figure 6. Figure 6 illustrates that a
plurality of wavelength pairs, all centered on the same
wavelength (approximately 980 nm), can be used in the

15   algorithms. These algorithms are standard in near-IR
analysis techniques and are easily programmed into
suitable microprocessor circuitry by those skilled in
the art. The use of these single variable term
equations is highly desirable because it allows

20   simplified instrument calibration, thereby allowing the
production of low cost instruments.

The intercept constant K_o and the slope constant K_1
are initially determined for a "master unit" (which
employs components similar or identical to those of the

25   production units) by simple linear regression analyses
of known samples, i.e., optical readings are obtained
from the instrument being constructed for a
representative number of samples which have been
previously accurately analyzed via another, well-

30   established technique, and the optical readings and
previously measured percentages are utilized to
calculate sets of constant values for blood glucose

content using a conventional regression algorithm in a
digital computer. The respective K_1 slope and K_0
intercept values are then programmed into each
production unit of the analyzing instrument so that
5   each production unit can directly compute values for
blood glucose from optical data readings.

Another class of usable near-IR standard
algorithms involves the use of multiple regression
terms. Such terms can be individual log 1/I terms or
10   can be a multiple number of first or second derivative
terms with or without a normalizing denominator. Such
multiple terms may provide additional accuracy, but
introduce much higher calibration expense which results
in a more expensive instrument.

15   Data on a plurality of physical parameters of the
body can also be utilized in conjunction with multiple
wavelength measurement of near-infrared interactance,
as in prior U.S. Patent No. 4,633,087, to improve the
accuracy of the present blood glucose measurements.
20   In use, the analysis instrument 10 is positioned
so that its flat bottom surface rests on the skin
directly above the prominent vein of the wrist of a
test subject. Light at the selected wavelengths
emerging from the instrument interacts with venous
25   blood of the subject and is detected by detector 28.
Detector 28 generates an electrical signal which is
processed as described above.

A key to accurate analysis is the ability of the
user to locate the transmitter and detector filter (or
30   window) directly over the prominent vein of the wrist.
The location device illustrated in Figure 3 greatly
facilitates this procedure. The device 50 is
constructed of, e.g., a plastic material and has an
overall length L equal to the length L of the analysis

instrument 10 of Figure 1. Two holes 51 are present in
the device and are located in the same relation as 14
and 19 in Figure 1, on midline 52, a distance l apart
corresponding to the distance l of Figure 1. The holes
5   51 permit observation of the prominent vein. When the
device is placed on the wrist and the vein is centered
in each hole 51, the wrist is marked (e.g. with a felt-
tipped pen) at notches 53. The location device is then
removed and replaced by the analysis instrument 10 with
10   assurance that the instrument is accurately disposed
directly over the vein.

An alternate procedure for practicing the
inventive method is accomplished by the use of fiber
optic light probes as seen in Figure 4. These probes
15   are connected with a known near-IR analysis instrument
such as the TREBOR-70 scanning spectrophotometer. A
probe 60 is placed over the prominent vein and
transmits near-IR energy of the desired wavelength(s).
The near-IR energy interacts with the blood
20   constituents and is collected by a second probe 62
placed over the vein a short distance l from first
probe 60. A detector associated with the analytical
instrument provides an electrical signal which is
processed, as described above, to reveal quantitative
25   information concerning blood glucose.

We have found that accurate quantitative analysis
of blood glucose levels can be made at a variety of
wavelengths with both interactance and transmittance
technologies. In the embodiment illustrated in Figures
30   2A and 2B near-IR light energy is transmitted through
the finger of the test subject and then detected by an
optical detector. As in all near-IR quantitative
analysis instruments, a combination of measurement
wavelengths is selected which emphasizes the glucose

absorption and removes the affect of interfering
absorption, for example, due to water, fat and protein.
Such selection is normally performed by computer search
studies. Figure 7 illustrates such a search study.

5   Figure 7 presents correlation coefficient versus
wavelength for an approximated first derivative
algorithm and illustrates that the use of the
wavelength pair of 980 ± (plus and minus) 35 nm
provides a high correlation between blood glucose and

10   absorption of near-IR energy at those two wavelengths.
        An example of one embodiment of the invention uses
IREDs which provide near-IR energy at two frequencies
which are, respectively, equidistant above and below
approximately 980 nm, i.e., they can be represented by

15   the formula 980 ± x nm. The value of x is not critical
so long as the two frequencies are centered on
approximately 980 nm. For example x can be a number
from 10 to 40.
        Figure 8A shows a plot of midpoint wavelength

20   versus correlation coefficient and illustrates a
midpoint wavelength for a wavelength pair to be
approximately 980 nm for a numerator, while Figure 8B
illustrates a midpoint wavelength to be approximately
908 nm for a denominator, of a O.D. / O.D. first

25   derivative division equation. The value of x was 35.
Figure 9 shows that an optimum wavelength for a
numerator in the first derivative division equation is
approximately 1013 nm (i.e., 980 + 35 nm). Figure 10
shows that there are many wavelength regions that can

30   provide midpoint wavelengths for use in the denominator
of the first derivative division equation when the
numerator utilizes 980 ± 35 nm wavelengths. Examples
of such regions are seen to be from 610 to 660 nm, from
910 to 980 nm and from 990 to 1080 nm.

Figures 11 and 12 illustrate optimum center
wavelengths for use in second derivative division
equations. Figure 11 shows via a plot of correlation
coefficient versus wavelength that the optimum

5   numerator center frequency is approximately 1020 nm.
Figure 12 shows that a denominator center frequency of
about 850 nm is optimum.

As seen in Figure 2A, a near-IR probe 100 is
adapted to be placed over the finger F of a test

10   subject and in this particular embodiment includes a
point source means of near-IR light energy comprised of
two IREDs 116 disposed within of an upper flange 110.
Each IRED is paired with a narrow bandpass optical
filter 123 and is optically isolated via opaque light

15   baffle 119. The inwardly-facing surface of flange 110
is provided with an optical optically clear window 114
for placement against the subject's finger.
Upper flange 110 is hinged about shaft 111 to
lower flange 120, and a spring 112 serves to maintain

20   the flanges in a closed position. An optical detector
128 is disposed in lower flange 120 opposite the near-
IR source 116. The detector is disposed behind an
optional window 129 which can be constructed of a
material which is either optically clear or which

25   excludes visible light yet permits near-IR light to
pass. A finger stop 103 helps place and maintain the
subject's finger in its proper position within the
probe 100. Each of the flanges is provided with light-
shielding barriers 113 (shown in phantom in Figure 2A)

30   to block ambient light from entering the probe.
In this embodiment the IREDs are pulsed, i.e.
energized in sequence, so that the detector 128
receives light transmitted from only one of the IREDs
at any one time. This pulsed IRED technology is

described in commonly owned U.S. Patent No. 4,286,327
which is incorporated by reference herein. In other
similar embodiments a group of IREDs (and optional
narrow bandpass filters) with identical wavelength
5   output can be pulsed.

Probe 100 is in electrical connection with a
processor unit which is schematically illustrated in
Figure 2A. The processor unit houses a power source,
signal amplifying, data processing and display
10   circuitry as described in connection with the
embodiment of Figure 1 and standard in near-IR analysis
instrumentation.

An alternate embodiment is seen in Figure 2B.
Here, probe 110 includes a single constant output IRED
15   116 installed behind an optional window 114. Light
transmitted through the finger is gathered by optical
funnel 112, which is constructed of a transparent
material, and detected by multiple detectors 128. The
detectors are optically isolated from one another by
20   opaque light baffle 119. Each detector is paired with
a narrow bandpass optical filter 123 and thus is set up
to detect only light within the narrow wavelength range
of its filter.

Near-IR point source means 116 can consist of one
25   or more IREDs of known bandwidth and center frequency
output or, as described above, can include a narrow
bandpass optical filter within the light path to
provide for the detection of only those wavelengths
which are of interest. Multiple wavelengths can be
30   utilized in transmission analysis and can be generated
via multiple IREDs provided they are consecutively
illuminated. Another approach is to use a single IRED
with multiple bandpass filters which are mechanically
moved through the light path as seen in Figure 5. A

18

third approach uses a single or group of IREDs capable of emitting a plurality of desired wavelengths with the use of multiple optical filters, each filter being married to a respective detector. Single IREDs which
5   emit two, three or four narrow bandwidths are commercially available.

In use, the finger of the test subject is inserted between the flanges 110 of the probe 100. Near-IR light energy is emitted by the point source means, is
10   transmitted through the finger and is detected by optical detector 128. The electrical signals produced by the detectors are transmitted via line 130 to a processor unit where the signal is amplified and data processed (using the above algorithm) as described in
15   connection with the apparatus of Figure 1. Blood glucose level is displayed on a readout device which preferably includes a digital display.

The accuracy of this preferred near-IR transmission embodiment can be further improved by
20   altering the algorithm to include finger thickness as a parameter. According to Lambert's law, energy absorption is approximately proportional to the square of the thickness of the object. The thickness of the test subject's finger can be quantified by installing a
25   potentiometer 140 between the flanges of the probe 100 as seen in Figures 2A and 2B. The output of the potentiometer, which is in electrical connection with the data processing circuitry, is indicative of finger thickness. A non-linear potentiometer can approximate
30   the T^2 value via its output alone so that a separate squaring calculation step is not required.

Although the invention has been described in connection with certain preferred embodiments, it is not limited to them. Modifications within the scope of

the following claims will be apparent to those skilled in the art. For example, accurate measurements can be obtained from parts of the body besides the wrist and the finger. The algorithm used to calculate blood
5   constituent concentration(s) can be altered in accordance with known near-infrared analytical techniques.

Claims:

1.   A near-infrared quantitative analysis
instrument for non-invasive measurement of blood
glucose in blood present in a body part of a subject,
5   comprising:

(a)   introducing means for introducing near-
infrared energy into blood present in a body part of a
subject;

(b)   detecting means for detecting near-
10   infrared energy emerging from the body part;

(c)   positioning means for positioning both
the near-infrared introducing means and the detecting
means closely adjacent to the body part; and

(d)   processing means for processing an
15   electrical signal produced by the detector means into a
second signal indicative of the quantity of glucose
present in the blood of the subject.

2.   An analysis instrument of claim 1 wherein
said positioning means includes a case, said
20   introducing means being disposed in a first chamber of
the case, said detecting means being disposed in a
second chamber of the case, said case comprising means,
separating said first and second chambers, for
preventing near-infrared energy from the introducing
25   means from impinging directly on the detector means.

3.   An analysis instrument of claim 2 wherein
said introducing means comprises generating means for
generating near-infrared energy and transmitting means
for transmitting said energy into the body part.

30   4.   An analysis instrument of claim 3 wherein
said generating means comprises an infrared emitting
diode.

5. An analysis instrument of claim 3 wherein said transmitting means comprises a lens for focusing said energy onto the body part.

6. An analysis instrument of claim 2 wherein said converting means comprises amplifier means and data processing means disposed in said second chamber.

7. An analysis instrument of claim 3 further comprising filter means, for selectively transmitting near-infrared energy, disposed between said generating and said transmitting means.

8. An analysis instrument of claim 4 wherein said infrared emitting diode produces a bandwidth centered on about 980 nanometers.

9. An analysis instrument of claim 7 for blood glucose measurement wherein said filter means selectively transmits near-infrared energy of between about 600 and about 1100 nanometers.

10. An analysis instrument of claim 1 wherein said positioning means comprises means for marking a position for said instrument over a blood vessel of a subject.

11. An analysis instrument of claim 1 wherein said positioning means comprises means for positioning said introducing means closely adjacent to one side of the body part and for positioning said detecting means closely adjacent to an opposite side of the body part whereby near-IR energy emitted by said introducing means is transmitted through said body part and is subsequently detected by said detector means.

12. An analysis instrument of claim 11 wherein said positioning means further comprises measuring means for measuring the thickness of the body part.

13. An analysis instrument of claim 12 wherein said measuring means further comprises means for

providing an electrical signal indicative of the thickness of the body part.

14. An analysis instrument of claim 13 wherein said means for providing an electrical signal comprises

5   a variable resistor.

15. An analysis instrument of claim 11 wherein said introducing means comprises an infrared emitting diode.

16. An analysis instrument of claim 15 wherein

10   said infrared emitting diode produces a bandwidth centered on about 980 nanometers.

17. A non-invasive method of quantitatively analyzing for blood glucose the blood of a subject, comprising:

15   (a)   introducing near-infrared energy into blood within a body part of the subject;

        (b) detecting near-infrared energy emerging from the subject, the detector providing an electrical signal upon detecting said emerged

20   energy, and

        (c) processing the electrical signal to provide a second signal indicative of the amount of glucose present in the blood.

18. A method of claim 17 wherein said near-

25   infrared energy is between about 600 and 1100 nanometers.

19. A non-invasive near-IR interactance method of quantitatively analyzing for glucose in venous or arterial blood of a subject, comprising:

30   (a)   introducing near-infrared energy into a vein or artery of the subject by placing an introducing means closely adjacent to said vein or artery, said energy interacting with

the blood glucose of the subject and then emerging from the vein or artery;

(b) detecting the emerged near-infrared radiation with a detector positioned closely adjacent to the vein or artery and along the vein or artery a predetermined distance from the transmitter, the detector providing an electrical signal upon detecting said radiation, and

(c) processing the electrical signal to provide a second signal indicative of the amount of glucose present in the blood.

20. A method of claim 19 wherein said near-infrared radiation is between about 600 and 1100 nanometers.

21. A non-invasive method of quantitatively analyzing for glucose in venous or arterial blood of a subject, comprising:

(a) marking a position for locating a quantitative analysis instrument over a vein or artery of a subject with a marking device;

(b) aligning a quantitative analysis instrument with said marked position, said instrument including a means for introducing near-infrared radiation into venous or arterial blood of the subject, a detector for detecting near-infrared energy following interactance with blood glucose, and means for processing a signal provided by the detector into a display indicative of blood glucose content;

(c) introducing near-infrared radiation into said blood;

(d) detecting near-infrared radiation following interactance with blood glucose; and

(e)   displaying results indicative of the blood glucose level based on said detected near-infrared radiation.

22.   A non-invasive near-IR transmission method for the quantitative analysis of blood glucose comprising:

(a)   introducing near-IR energy into one side of a blood-containing body part,

(b)   detecting with a detector means near-IR energy emerging from an opposite side of the body part, and

(c)   processing a signal provided by the detector means into a second signal indicative of blood glucose content.

23.   A method of claim 22 wherein said near-infrared energy is between about 600 and 1100 nanometers.

AMENDED CLAIMS
[received by the International Bureau
on 11 June 1990 (11.06.90);
original claim 22 cancelled; claims 1,11 amended;
original claims 2-4,6-9,12,13,17,21 and 23 replaced
by new claims bearing the same numbers; new claims
24-33 added (7 pages)]

1.   A near-infrared quantitative analysis instrument for
non-invasive measurement of blood glucose in blood present in
a body part of a subject, comprising:

(a)   means for introducing near-infrared energy into
5 blood present in a body part of a subject;

(b)   a near-infrared detector for detecting near-
infrared energy within the range of about 600 to 1110
nanometers emerging from the body part and for providing a
signal upon detection of near-infrared energy within said
10 range emerging from the body part;

(c)   means for positioning both the near-infrared
introducing means and the near-infrared detector closely
adjacent to the body part so that near-infrared energy
detected by the detector corresponds to blood glucose level in
15 said body part; and

(d)   means for processing the signal produced by the
detector into a second signal indicative of the quantity of
glucose present in the blood of the subject.

2.   An analysis instrument of claim 1 further including
means for preventing near-infrared energy from the introducing
means from impinging directly on the detector.

3.   An analysis instrument of claim 2 wherein said
introducing means includes a near-infrared energy source and
transmitting means for transmitting said energy into the body
part.

4.　An analysis instrument of claim 3 wherein said source comprises at least one infrared emitting diode.

5.　An analysis instrument of claim 3 wherein said transmitting means comprises a lens for focusing said energy onto the body part.

6.　An analysis instrument of claim 2 wherein said processing means comprises amplifier means for amplifying the signal provided by said detector, and data processing means for converting the signal from the detector into said second

5　signal.

7.　An analysis instrument of claim 1 wherein said introducing means includes a near infrared source and a filter for selectively transmitting near-infrared energy which filter is disposed between said source and said body part.

8.　An analysis instrument of claim 7 for blood glucose measurement wherein said filter selectively transmits near-infrared energy of between about 600 and about 1100 nanometers.

9.　An analysis instrument of claim 1 wherein said introducing means provides a bandwidth centered on about 980 nanometers.

10.　An analysis instrument of claim 1 wherein said positioning means comprises means for marking a position for said instrument over a blood vessel of a subject.

11.　An analysis instrument of claim 1 wherein said positioning means comprises means for positioning said introducing means closely adjacent to one side of the body

part and for positioning said detector closely adjacent to an opposite side of the body part whereby near-IR energy emitted by said introducing means is transmitted through said body part and detected by said detector.

12.   An analysis instrument of claim 11 wherein the positioning means positions the introducing means and the detector on opposite sides of a finger.

13.   An analysis instrument of claim 12 further including means for measuring the thickness of the body part and for providing a signal indicative of the thickness of the body part.

14.   An analysis instrument of claim 13 wherein said means for providing an electrical signal comprises a variable resistor.

15.   An analysis instrument of claim 11 wherein said introducing means comprises an infrared emitting diode.

16.   An analysis instrument of claim 15 wherein said infrared emitting diode produces a bandwidth centered on about 980 nanometers.

17.   An analysis instrument of claim 11 wherein said introducing means includes a near infrared source and a filter for selectively transmitting near-infrared energy which filter is disposed between said source and said body part.

18.   An analysis instrument of claim 17 for blood glucose measurement wherein said filter selectively transmits near-infrared energy of between about 600 and about 1100 nanometers.

19. The analysis instrument of claim 11 further including at least one filter for selectively transmitting near-infrared energy, which filter is disposed between the detector and said body part.

20. An analysis instrument of claim 19 for blood glucose measurement wherein said filter selectively transmits near-infrared energy of between about 600 and about 1100 nanometers.

21. A non-invasive method for quantitatively analyzing blood glucose in blood of a subject, comprising:

(a)   introducing at least one pair of wavelengths of near infrared energy into blood within a body part of the subject, said pair being centered on a wavelength within the range of about 600 to 1100 nanometers;

(b)   detecting near-infrared energy emerging from the subject with a detector which provides a signal upon detecting said energy emerging from the subject; and

(c)   processing the signal to provide a second signal indicative of the amount of glucose present in the blood of the subject.

23. The method of claim 21 wherein near infrared energy centered on about 980 nanometers is introduced into the blood within said body part.

24. The analysis instrument of claim 1 wherein said introducing means provides at least one wavelength pair centered on about 980 nanometers.

25. The method of claim 21 wherein at least one pair of wavelengths of near infrared energy centered on about 980 nanometers is introduced into the blood within said body part.

26. The analysis instrument of claim 1 wherein the signal processing means processes the signal according to the formula

$$C = K_0 + K_1 [\log 1/I_G - \log 1/I_H]$$

wherein C is concentration of glucose present in the blood, K_0

5   is an intercept constant, K_1 is line slope of

$$[\log 1/I_G - \log 1/I_H]$$

and $\log 1/I_G$ and $\log 1/I_H$ each represent an optical density value at corresponding wavelengths G and H.

27. The analysis instrument of claim 1 wherein the signal processing means processes the signal according to the formula

$$C = K_0 + K_1 [\log 1/I_A - 2*\log 1/I_B + \log 1/I_C]$$

wherein C is concentration of glucose present in the blood, K_0

5   is an intercept constant, K_1 is line scope of

$$[\log 1/I_A - 2*\log 1/I_B + \log 1/I_C]$$

and $\log 1/I_A$, $\log 1/I_B$, and $\log 1/I_C$ each represent an optical density value at corresponding wavelengths A, B and C.

28. The analysis instrument of claim 1 wherein the signal process means processes the signal according to the formula

$$C = K_0 + K_1 \frac{[\log 1/I_G - \log 1/I_H]}{[\log 1/I_I - \log 1/I_J]}$$

5

wherein C is concentration of glucose present in the blood, K_0 is an intercept constant, K_1 is line slope of

$$\frac{[\log 1/I_G - \log 1/I_H]}{[\log 1/I_I - \log 1/I_J]}$$

10

and log $1/I_G$, log $1/I_H$, log $1/I_I$ and log $1/I_J$ each represent an optical density value at corresponding wavelengths G, H, I and J.

29. The analysis instrument of claim 1 wherein the signal processing means processes the signal according to the formula

$$C = K_0 + K_1 \frac{[\log 1/I_A - 2*\log 1/I_B + \log 1/I_C]}{[\log 1/I_D - 2*\log 1/I_E + \log 1/I_F]}$$

5

wherein C is concentration of glucose present in the blood, K_0 is an intercept constant, K_1 is the line slope of

$$\frac{[\log 1/I_A - 2*\log 1/I_C]}{[\log 1/I_D - 2*\log 1/I_E + \log 1/I_F]}$$

10

and log $1/I_A$, log $1/I_B$, log $1/I_C$, log $1/I_D$, log $1/I_E$, and log $1/I_F$ each represent an optical density value at corresponding wavelengths A, B, C, D, E and F.
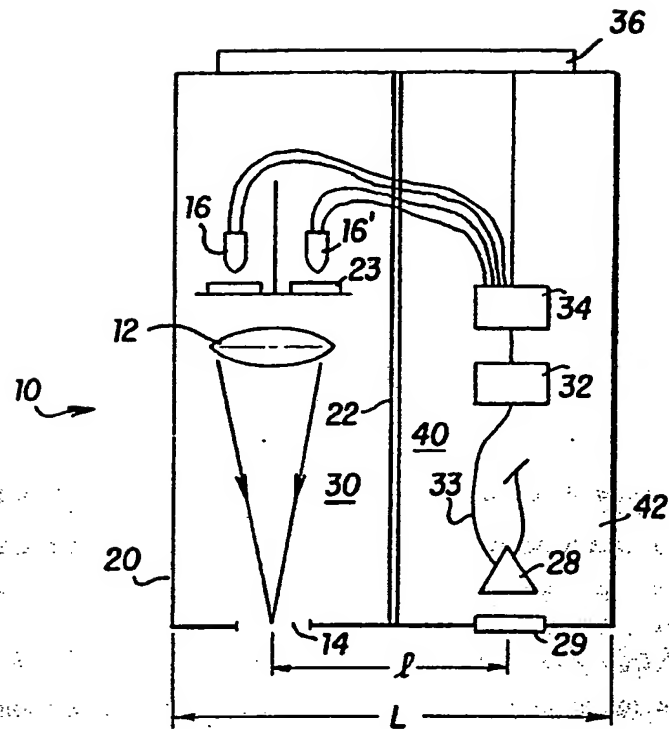
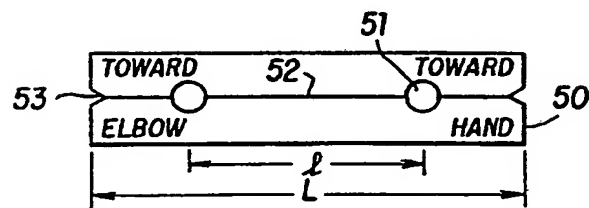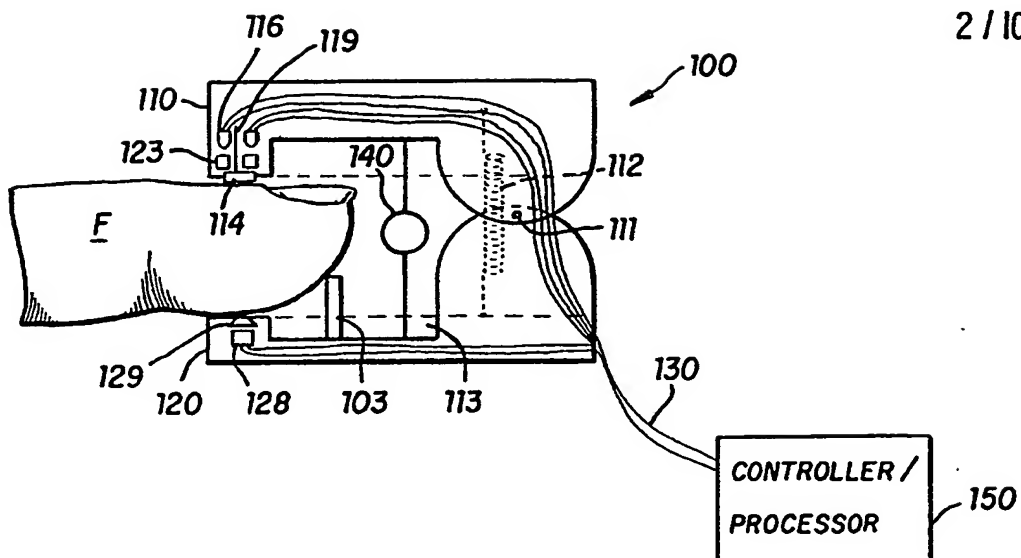30. The method of claim 21 wherein the signal is processed according to the formula

$$C = K_0 + K_1 [\log 1/I_G - \log 1/I_H]$$

wherein C is concentration of glucose present in the blood, K_0 is an intercept constant, K_1 is line slope of

$$[\log 1/I_G - \log 1/I_H]$$

and log $1/I_G$ and log $1/I_H$ each represent an optical density value at corresponding wavelengths G and H

31. The method of claim 21 wherein the signal processing means processes the signal according to the formula

$$C = K_0 + K_1 [\log 1/I_A - 2*\log 1/I_B + \log 1/I_C]$$

wherein C is concentration of glucose present in the blood, K_0 is an intercept constant, K_1 is line slope of

$$[\log 1/I_A - 2*\log 1/I_B + \log 1/I_C]$$

and $\log 1/I_A$, $\log 1/I_B + \log 1/I_C]$

and $\log 1/I_A$, $\log 1/I^m{}_B$, and $\log 1/I_C$ each represent an optical density value at corresponding wavelengths A, B and C.

32. The method of claim 21 wherein the signal processing means processes the signal according to the formula

5 $$C = K_0 + K_1 \frac{[\log 1/I_G - \log 1/I_H]}{[\log 1/I_I - \log 1/I_J]}$$

wherein C is concentration of glucose present in the blood, K_0 is an intercept constant, K_1 is line slope of

10 $$\frac{[\log 1/I_G - \log 1/I_H]}{[\log 1/I_I - \log 1/I_J]}$$

and $\log 1/I_G$, $\log 1/I_H$, $\log 1/I_I$ and $\log 1/I_J$ each represent an optical density value at corresponding wavelengths G, H, I and J.

33. The method of claim 21 wherein the signal processing means processes the signal according to the formula

5 $$C = K_0 + K_1 \frac{[\log 1/I_A - 2*\log 1/I_B + \log 1/I_C]}{[\log 1/I_D - 2*\log 1/I_E + \log 1/I_F]}$$

wherein C is concentration of glucose present in the blood, K_0 is an intercept constant, K_1 is the line slope of

10 $$\frac{[\log 1/I_A - 2*\log 1/I_B + \log 1/I_C]}{[\log 1/I_D - 2*\log 1/I_E + \log 1/I_F]}$$

and $\log 1/I_A$, $\log 1/I_B$, $\log 1/I_C$, $\log 1/I_D$, $\log 1/I_E$, and $\log 1/I_F$ each represent an optical density value at corresponding wavelengths A, B, C, D, E and

1 / 10

FIG. 1

FIG. 3
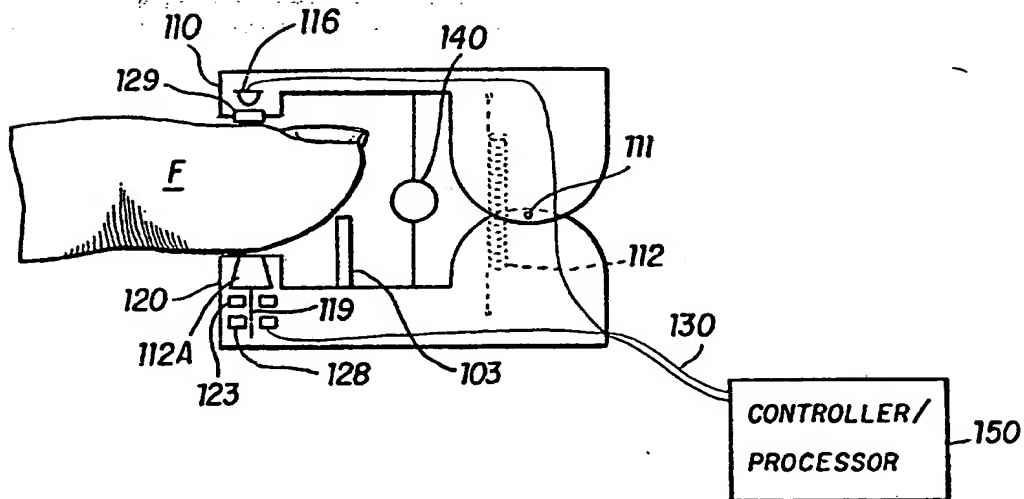
FIG. 2A

FIG. 2B

3 / 10

FIG. 4

17

LIGHT SOURCE

LENS

WIDEBAND LIGHT BEAM

23'

TILTING FILTER
WAVELENGTH VARIES AS FILTER TURNS

NARROWBAND LIGHT BEAM

OPTICAL DETECTOR

FIG. 5A

LIGHT
SOURCE 17'

23"

DISK WITH
OPTICAL FILTERS
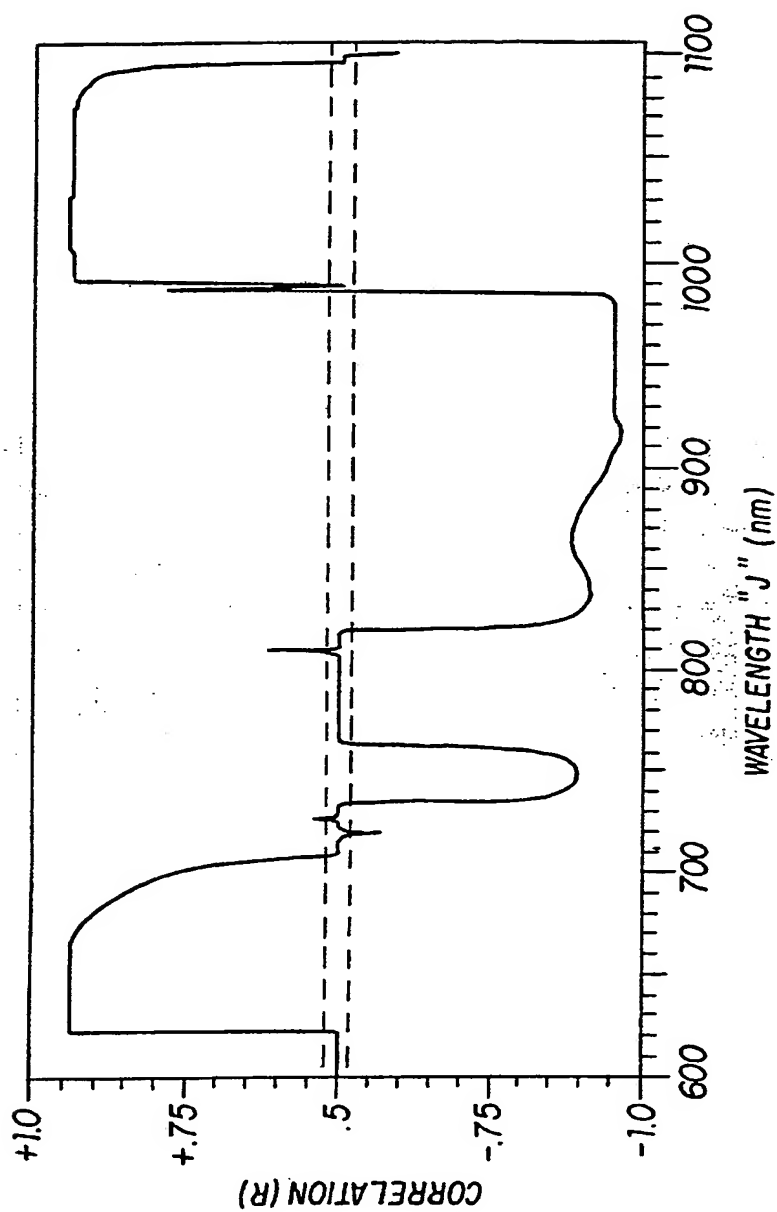
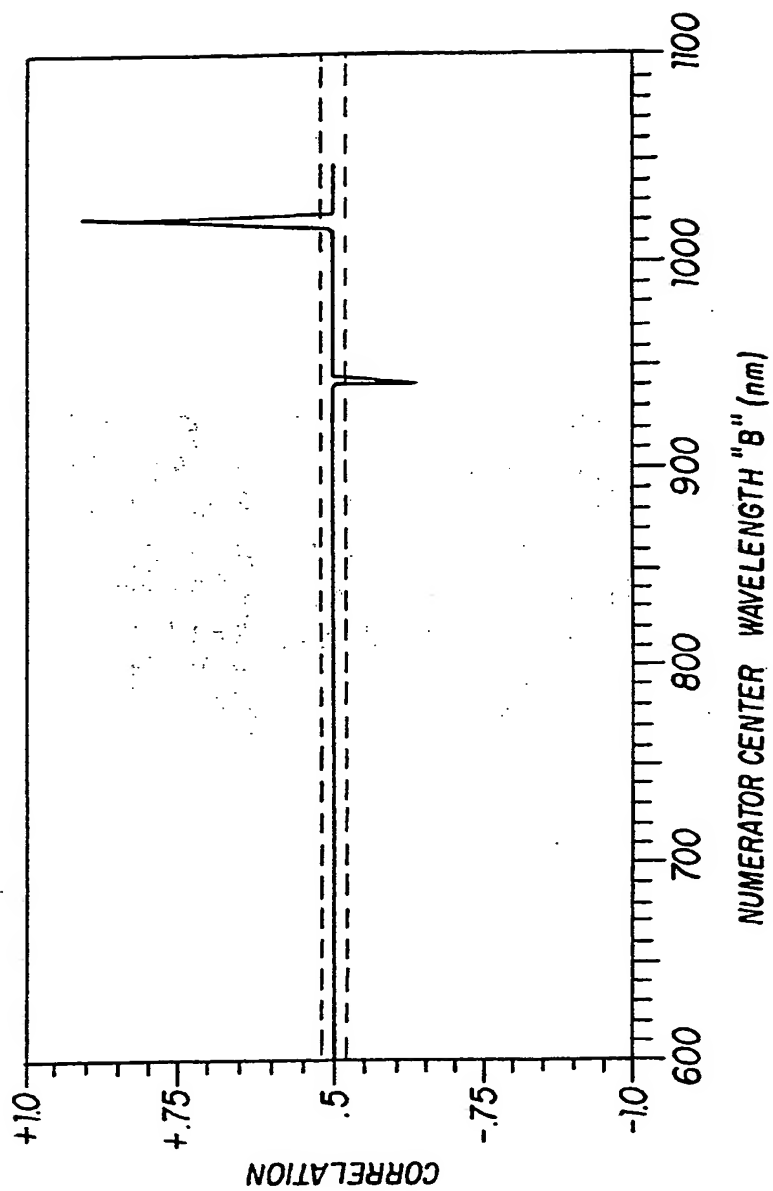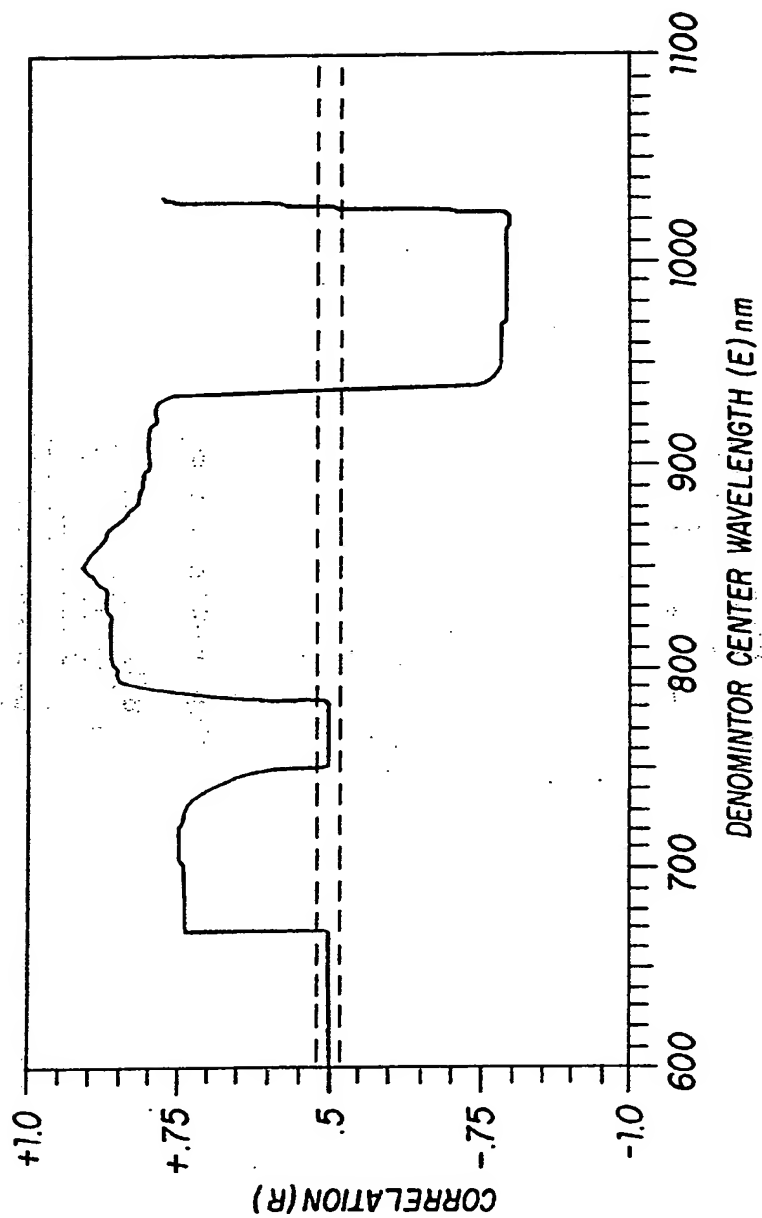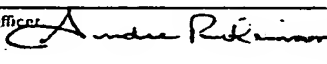OPTICAL DETECTOR

FIG. 5B

5 / 10
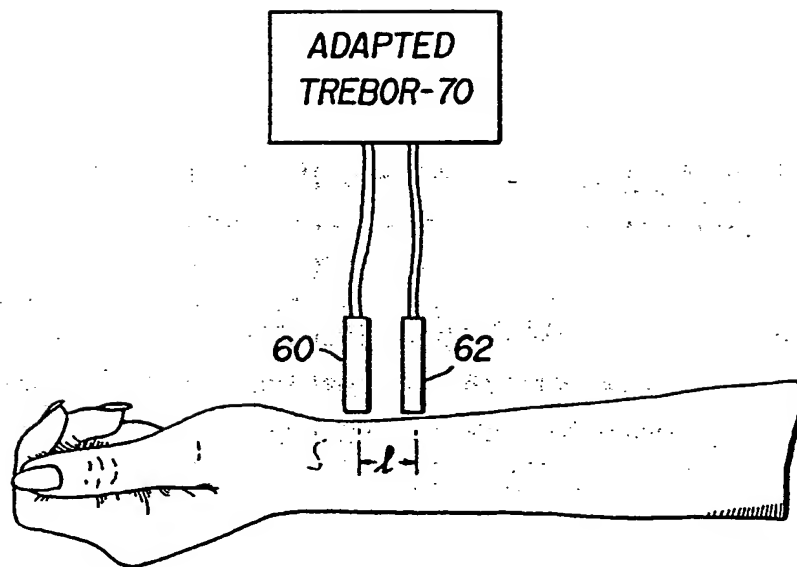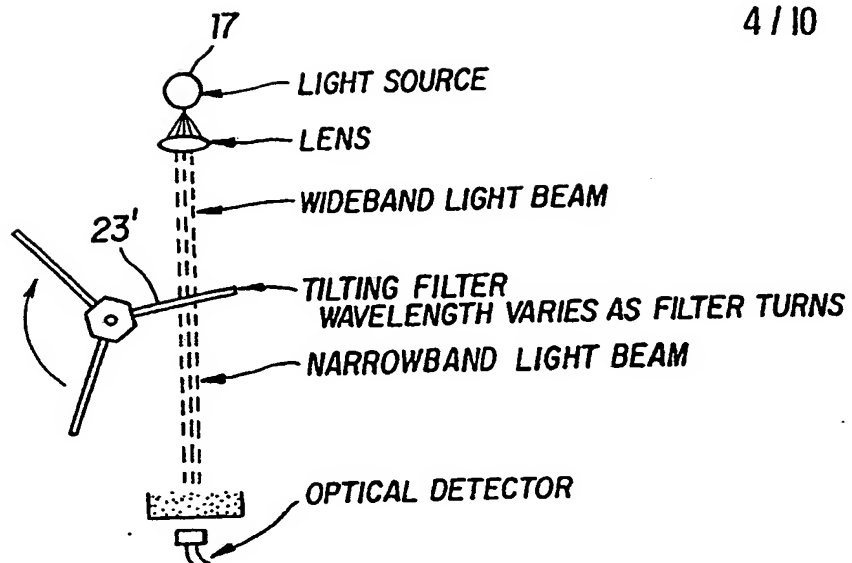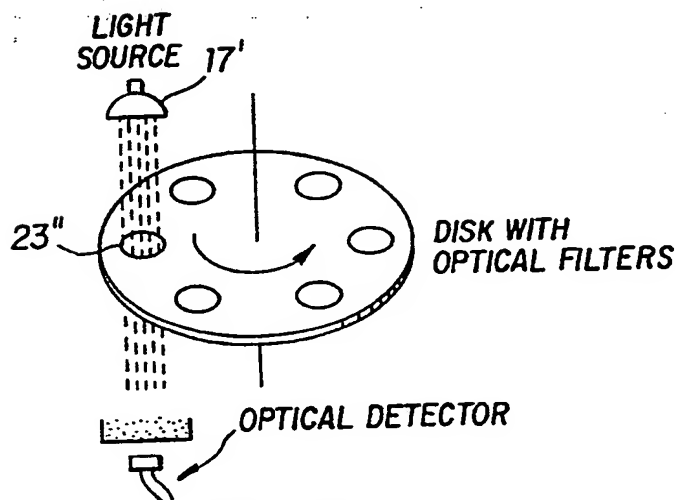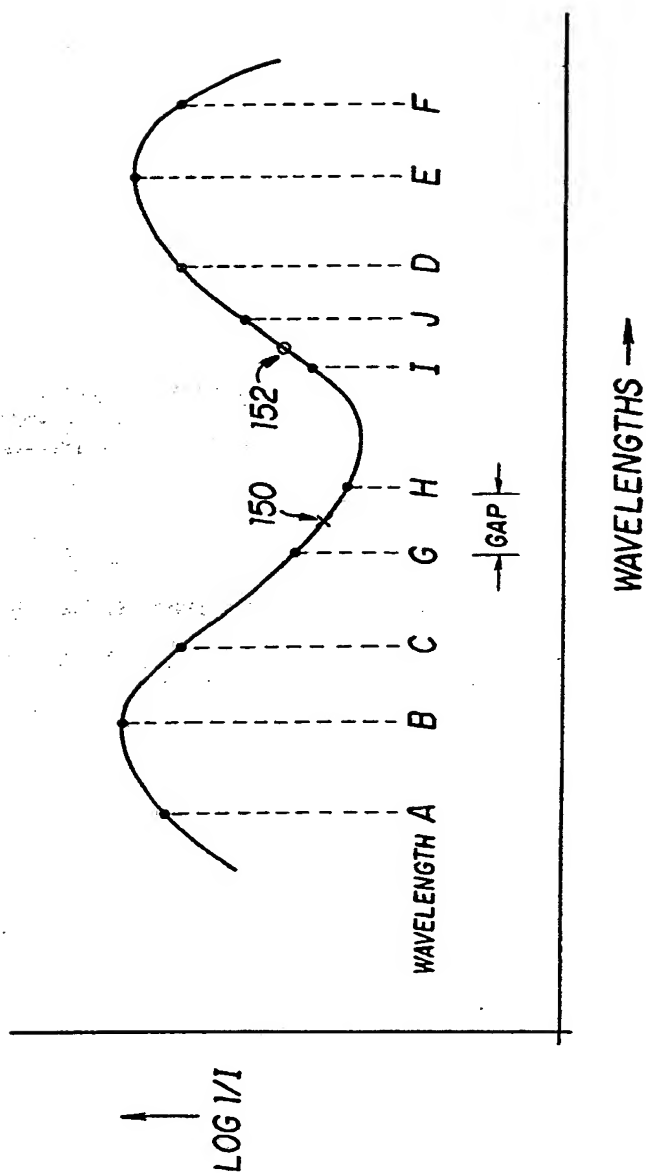
FIG. 6
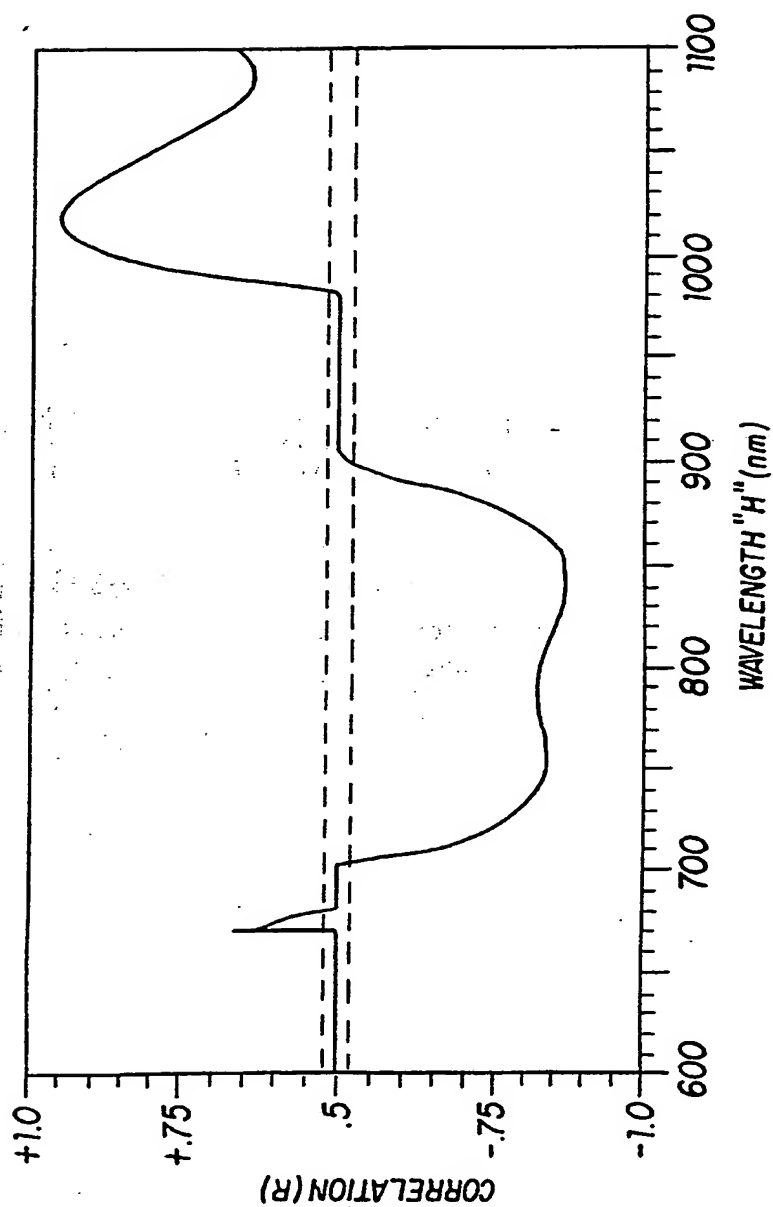
FIG.7
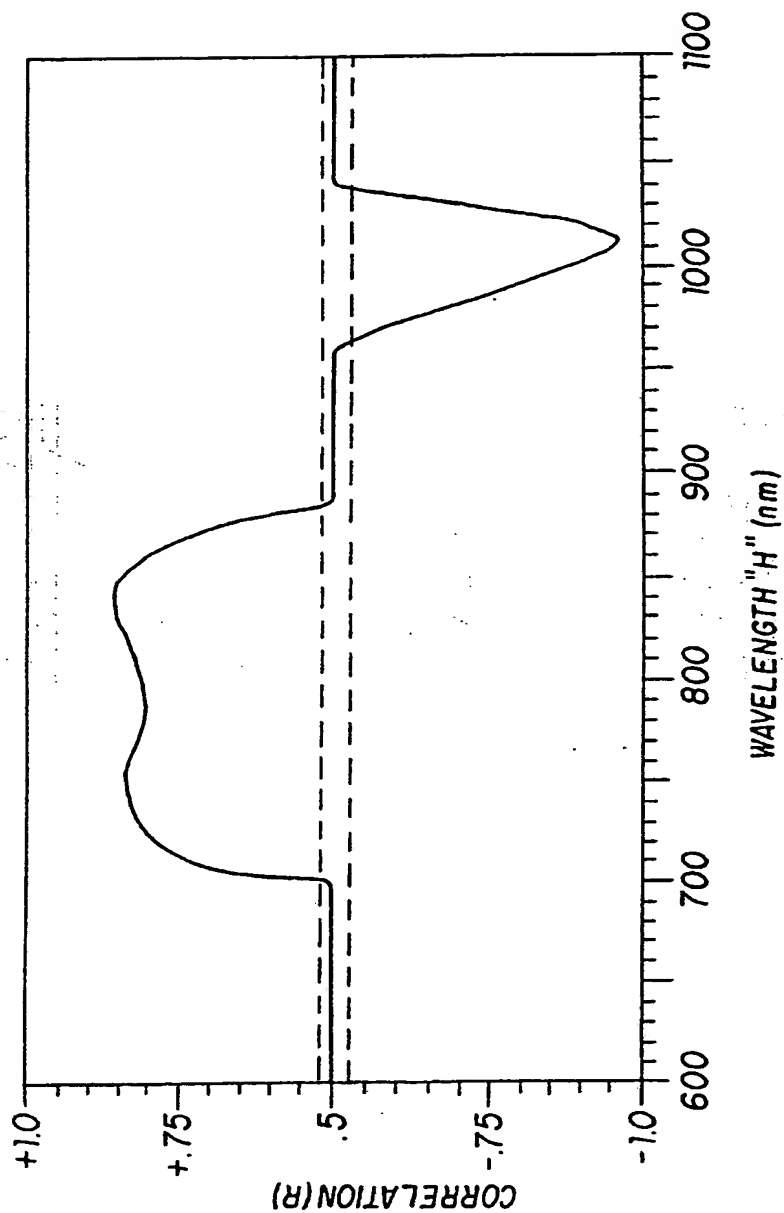
FIG. 8

FIG.9

FIG. 10

FIG. 11

INTERNATIONAL SEARCH REPORT

International Application No. **PCT/US90/00394**

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) 6
According to International Patent Classification (IPC) or to both National Classification and IPC
INT CL^5 ; A61B 5/00; A61B 5/14; G01N 21/35   U.S. CL. 250/339,341

II. FIELDS SEARCHED

Minimum Documentation Searched 7	
Classification System	Classification Symbols
U.S.	250/339,341; 356/39; 128/633

Documentation Searched other than Minimum Documentation   to the Extent that such Documents are Included in the Fields Searched 8

III. DOCUMENTS CONSIDERED TO BE RELEVANT 9

Category *	Citation of Document, 11 with indication, where appropriate, of the relevant passages 12	Relevant to Claim No. 13
Y	EP, A1, 0160 768 (DAHNE et al) 13 NOVEMBER 1985 See the entire document.	1-23
Y	DE, A1, 3541 165 (SCHMIDTKE et al) 27 MAY 1987 See the entire document.	1-23
Y	US,A, 4,260,262 (WEBSTER) 07 APRIL 1981 See columns 3 and 4.	1-23

* Special categories of cited documents: 10

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
09 MARCH 1990	**1 0 APR 1990**
International Searching Authority	Signature of Authorized Officer
ISA/US	RICHARD HANIG

Form PCT/ISA/210 (second sheet) (Rev.11-87)